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(54) Title: HETEROCYCLIC COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

The invention is directed toward substituted heteroaromatic compounds which are protein tyrosine kinase inhibitors, in particular to substituted quinolines and quinazolines. Methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of psoriasis, fibrosis, atherosclerosis, restenosis, auto-immune disease, allergy, asthma, transplantation rejection, inflammation, thrombosis, nervous system diseases, and cancer.

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HETEROCYCLIC COMPOUNDS AND PAHRMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to a series of substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to quinoline and quinazoline derivatives which exhibit protein tyrosine kinase inhibition.

Protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A.F.Wilks, Progress in Growth Factor Research, 1990 (2), 97-111). Tyrosine kinases can be broadly classified as growth factor receptor (e.g. EGF-R, PDGF-R, FGF-R and erbB-2) or non-receptor (e.g. src, bcr-abl) kinases. Inappropriate or uncontrolled activation of many of these kinases i.e. aberrant tyrosine kinase activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth.

Aberrant activity of protein tyrosine kinases such as c-erbB-2, c-src, p56lck, EGF-R, PDGF-R, and zap70 have been implicated in human malignancies. Aberrant EGF-R activity has, for example, been implicated in cancers of the head and neck, and aberrant c-erbB-2 activity in breast, ovarian, non-small cell lung, pancreatic, gastric and colon cancers. Inhibitors of protein tyrosine kinase should therefore provide a treatment for tumours such as those outlined above.

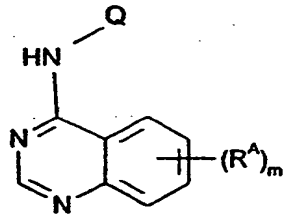
Aberrant protein tyrosine kinase activity has also been implicated in a variety of other disorders: psoriasis, (Dvir et al, J.Cell.Biol; 1991, 113, 857-865), fibrosis, atherosclerosis, restenosis, (Buchdunger et al, Proc.Natl.Acad.Sci. USA; 1991, 92, 2258-2262), auto-immune disease, allergy, asthma, transplantation rejection (Klausner and Samelson, Cell; 1991, 64, 875-878), inflammation (Berkois, Blood; 1992, 79(9), 2446-2454), thrombosis (Salari et al, FEBS; 1990, 263(1), 104-108) and nervous system diseases (Ohmichi et al, Biochemistry, 1992, 31, 4034-4039). Inhibitors of the specific tyrosine kinases involved in these dis ases eg PDGF-r in restenosis and EGF-r in psoriasis, should lead to novel therapies for such

disorders. P56lck and zap 70 are indicated in disease conditions in which T cells are hyperactive e.g. rheumatoid arthritis, autoimmune disease, allergy, asthma and graft rejection.

Published European Patent numbers 0520722, 0566226, 0602851, 0635498 and 0635507 disclose quinazoline derivatives and their preparation for use in the treatment of cancer. The above citations note that receptor tyrosine kinases in general, which are important in the transmission of biochemical signals initiating cell replication, are frequently present in common human cancers such as breast cancer (Sainsbury *et al* Brit. J. Cancer 1988, 58, 458). These citations also state that tyrosine kinase activity is rarely detected in normal cells and it is suggested that inhibitors of receptor tyrosine kinase should be of value as inhibitors of the growth of mammalian cancer cells (Yaish *et al.* Science, 1988, 242, 933). The above citations therefore have the common aim of providing quinazoline derivatives which inhibit tyrosine kinases and envisage that the quinazoline derivatives should possess anti-cancer activity against a wide range of cancers.

Such broad spectrum inhibition of tyrosine kinase may not provide optimal treatment of the tumour, and could in certain cases even be deterimental to subjects since tyrosine kinases provide an essential role in the normal regulation of cell growth.

EP0602851 discloses quinazoline derivatives of the formula (1) :

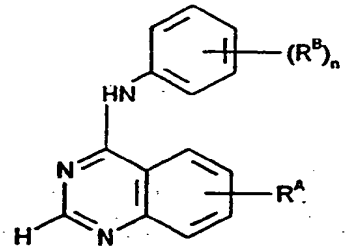


(1)

wherein m is 1, 2 or 3 and each R^A includes hydroxy, amino, ureido, hydroxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C) alkoxy and (1-3C) alkenedioxy; and Q is a 9 or 10-membered bicyclic heterocyclic moiety containing

one or two nitrogen atoms and optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur, or Q is a 9 or 10-membered bicyclic aryl moiety, the heterocyclic or aryl moiety optionally bearing one or two substituents selected from halogeno, hydroxy, oxo, amino, nitro, carbamoyl, (1-4C) alkyl, (1-4C) alkoxy, (1-4C) alkylamino, di-[(1-4C) alkyl]amino and (2-4C) alkanoylamino. The compounds are claimed to be inhibitors of the EGF tyrosine kinase receptor and other unspecified tyrosine kinases.

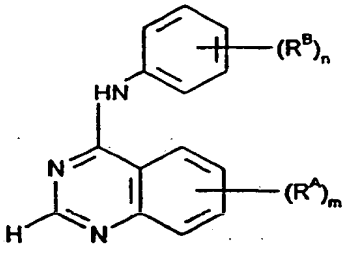
European Patent Application 0520722A discloses a class of quinazoline derivatives having antitumour activity and having the formula (2)



(2)

wherein, for example, R^A is hydrogen, trifluoromethyl or nitro, n is 1 and R^B is halogeno, trifluoromethyl, nitro, cyano, (1-4C)alkyl, (1-4C)alkoxy, N-(1-4C)alkylamino, N,N-di-((1-4C)alkyl)amino, (1-4C)alkylthio, (1-4C)alkylsulphinyl or (1-4C)alkylsulph- onyl. These compounds are claimed to be inhibitors of the EGF tyrosine kinase receptor and other unspecified tyrosine kinases.

EP 0566 226A discloses quinazoline derivatives of the formula (3):

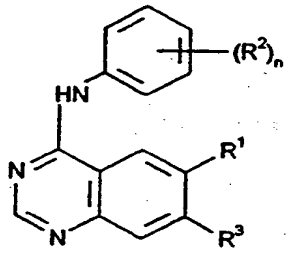


(3)

wherein m is 1, 2 or 3 and each R^A includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C) alkoxycarbonyl, N(1-4C) alkylcarbamoyl, N,N-di[(1-

4C)alkyl]carbamoyl, hydroxyamino, (1-4C) alkylamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy and (1-3C)alkenedioxy; n is 1 or 2 and each R^B includes; hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C) alkyl. The compounds are claimed to be inhibitors of the EGF tyrosine kinase receptor and other unspecified tyrosine kinases.

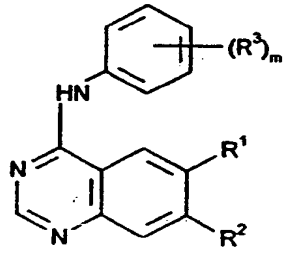
EP0635498 discloses quinazolines of the formula (4),



(4)

wherein R^1 includes hydroxy, amino, hydroxyamino, (1-4C)alkoxy, (1-4C) alkylamino and di-[(1-4C)alkyl]amino; R^2 includes independently hydrogen, hydroxy, halogeno, (1-4C)alkyl, (1-4C)alkoxy or (2-4C) alkanoylamino; n is 1, 2 or 3; and R^3 is halogeno.

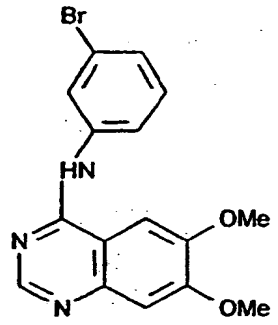
EP0635507 discloses tricyclic derivatives of the formula (5) :



(5)

wherein R^1 and R^2 together form specified optionally substituted groups containing at least one heteroatom so as to form a 5 or 6 membered ring, and R^3 includes independently hydrogen, hydroxy, halogeno, (1-4C)alkyl, (1-4C) alkoxy di-[(1-4C)alkyl]amino, or (2-4C)alkanoylamino.

Selective inhibition of the EGF receptor is, however, disclosed by Fry et al (Science, 265, 1093 (1994)). This citation discloses that the compound of formula:



is a highly selective inhibitor of the EGF receptor tyrosine kinase at picomolar concentrations while inhibiting other tyrosine kinases only at micromolar or higher concentrations. However, there is no disclosure of any compounds which are selective in their inhibition of tyrosine kinases other than EGF.

It is therefore a general object of the present invention to provide compounds suitable for the treatment of disorders mediated by protein tyrosine kinase activity, and in particular treatment of the above mentioned disorders. In addition to the treatment of tumours, the present invention envisages that other disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity

It is another object of the present invention to provide compounds which preferentially inhibit protein tyrosine kinases, such as c-erbB-2, c-erbB-4, c-src, p56lck, EGF-R, fyn, cdk2, PDGF-R, and zap70 protein tyrosine kinases. In other words, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a preferential manner.

A further object of the present invention is to provide compounds useful in the treatment of protein tyrosine kinase related diseases which minimise undesirable side-effects in the recipient.

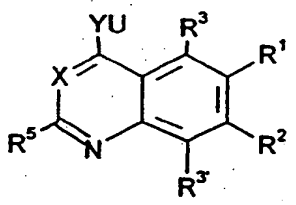
The present invention relates to certain quinoline and quinazoline derivatives which may be used to treat disorders mediated by protein tyrosine kinases and in particular have anti-cancer properties. More particularly, the compounds of the present invention are potent inhibitors of protein tyrosine kinases such as c-erbB-2, c-erbB-4, EGF-R, c-src, p56lck, fyn, cdk2, PDGF, and zap 70 thereby allowing chemical management of particular diseased tissues.

The present invention envisages, in particular, the treatment of human malignancies, for example breast, stomach, ovary, colon, lung and pancreatic tumours, especially those driven by c-erbB-2, using the compounds of the present invention. For example, the invention includes compounds which are highly active against the c-erbB-2 protein tyrosine kinase in preference to the EGF receptor kinase hence allowing treatment of c-erbB-2 driven tumours.

More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.

Certain compounds of the present invention, for example 4-(1-benzyl-5-indolylamino)-6,7-dimethoxyquinazoline and 4-(1-benzyl-5-indolylamino)-quinazoline have the unexpected advantage of being highly selective for c-erbB-2 over EGF, in contrast to compounds of the prior art which show little activity towards c-erbB-2 and no selectivity towards this tyrosine kinase. In the above case, the 4-(5-indolylamino)-6,7-dimethoxyquinazoline inhibits EGF to a much greater extent than it inhibits c-erbB-2, and the c-erbB-2 activity is relatively poor. The applicant has found that by appropriate substitution of the mono or bicyclic ring system, compounds of the invention may be synthesised which exhibit completely rev rsed tyrosine kinase selectivity from that which would be exp cted from the prior art, with the activity of the compounds of the present invention providing a further advantageous feature. For this reason, such compounds are expected to find utility in the treatment of a number of disorders, and in particular the tumours driven by c-erbB-2 mentioned above.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein;
X is N or CH;
Y is a group $W(CH_2)$, $(CH_2)W$ or W in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group;
U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S, wherein the ring system is substituted by at least one independently selected R^6 group and is optionally substituted by at least one independently selected R^4 group;
R^1, R^2, R^3 and $R^{3'}$ are the same or different and are each selected from amino, hydrogen, halogen, hydroxy, nitro, carboxy, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkoxyl, C_{4-8} alkylcyclo alkoxy, C_{1-8} alkoxycarbonyl, N-C_{1-4} alkylcarbamoyl, N,N-di-[C_{1-4} alkyl]carbamoyl, hydroxyamino, C_{1-4} alkoxyamino, C_{2-4} alkanoyloxyamino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-C_{1-4} alkylpiperazin-1-yl, C_{1-8} alkylthio, arylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, arylsulphonyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{2-4} alkanoyloxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, carboxy-C_{1-4} alkyl, C_{1-4} alkoxycarbonyl-C_{1-4}-alkyl,carbamoyl-C_{1-4} alkyl, N-C_{1-4} alkylcarbamoyl-C_{1-4}alkyl, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4}alkyl, amino-C_{1-4} alkyl, C_{1-4} alkylamino-C_{1-4} alkyl, di-[C_{1-4} alkyl]amino-C_{1-4} alkyl, piperidino-C_{1-4} alkyl, morpholino-C_{1-4} alkyl, piperazin-1-yl-C_{1-4} alkyl, 4-C_{1-4} alkylpiperazin-1-yl-C_{1-4} alkyl, hydroxy-C_{2-4} alkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkoxy-C_{1-4} alkyl, hydroxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, hydroxy-C_{2-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylthio-C_{1-4} alkyl, phenoxy-

C_{1-4} alkyl, anilino-C_{1-4} alkyl, phenylthio-C_{1-4} alkyl, cyano-C_{1-4} alkyl, halogeno-C_{2-4} alkoxy, hydroxy-C_{2-4} alkoxy, C_{2-4} alkanoyloxy-C_{2-4} alkoxy, C_{1-4} alkoxy-C_{2-4} alkoxy, carboxy-C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl-C_{1-4} alkoxy, carbamoyl-C_{1-4} alkoxy, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkoxy, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkoxy, amino-C_{2-4} alkoxy, C_{1-4} alkylamino-C_{2-4} alkoxy, di-[C_{1-4} alkyl]amino-C_{2-4} alkoxy, C_{2-4} alkanoyloxy, hydroxy-C_{2-4} alkanoyloxy, C_{1-4}alkoxy-C_{2-4} alkanoyloxy, phenyl-C_{1-4} alkoxy, phenoxy-C_{2-4} alkoxy, anilino-C_{2-4} alkoxy, phenylthio-C_{2-4} alkoxy, piperidino-C_{2-4} alkoxy, morpholino-C_{2-4} alkoxy, piperazin-1-yl-C_{2-4} alkoxy, 4-C_{1-4} alkylpiperazin-1-yl-C_{2-4} alkoxy, halogeno-C_{2-4} alkylamino, hydroxy-C_{2-4} alkylamino, C_{2-4} alkanoyloxy-C_{2-4} alkylamino, C_{1-4} alkoxy-C_{2-4} alkylamino, carboxy-C_{1-4} alkylamino, C_{1-4} alkoxycarbonyl-C_{1-4} alkylamino, carbamoyl-C_{1-4} alkylamino, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkylamino, amino-C_{2-4} alkylamino, C_{1-4} alkylamino-C_{2-4} alkylamino, di-[C_{1-4}alkylamino-C_{2-4} alkylamino, phenyl-C_{1-4} alkylamino, phenoxy-C_{2-4} alkylamino, anilino-C_{2-4} alkylamino, phenylthio-C_{2-4} alkylamino, C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkylsulphonylamino, benzamido, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halogeno-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoylamino, C_{1-4} alkoxy-C_{2-4} alkanoylamino, carboxy-C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonyl-C_{2-4} alkanoylamino, carbamoyl-C_{2-4} alkanoylamino, N-C_{1-4} alkylcarbamoyl-C_{2-4} alkanoylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{2-4} alkanoylamino, amino-C_{2-4} alkanoylamino, C_{1-4} alkylamino-C_{2-4} alkanoylamino or di-[C_{1-4} alkyl]amino-C_{2-4} alkanoylamino, and wherein said benzamido or benzenesulphonamido substitutent or any anilino, phenoxy or phenyl group on a R^1 substituent may optionally bear one or two halogeno, C_{1-4}alkyl or C_{1-4}alkoxy substituents;

or any adjacent pair of R^1, R^2, R^3 and $R^{3'}$ together form an optionally substituted methylenedioxy or ethylenedioxy group;

each R^4 is independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, di-[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, di-[C_{1-4} alkyl] carbamoyl, carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro or trifluoromethyl;

R^5 is hydrogen, halogen, trifluoromethyl, C_{1-4} alkyl or C_{1-4} alkoxy;

each R^6 is independently a group ZR^7 wherein Z is joined to R^7 through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, $V(CRR')$, V(CHR) or V where R and R' are each C_{1-4} alkyl and in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, CH(OH), sulphonamide, amide, O, $S(O)_m$ or NR^b where R^b is hydrogen or R^b is C_{1-4} alkyl; and R^7 is an optionally substituted C_{3-6} cycloalkyl; or an optionally substituted 5, 6, 7, 8, 9 or 10 membered carbocyclic or heterocyclic moiety;

or R^6 is a group ZR^7 in which Z is NR^b, and NR^b and R^7 together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety.

In an embodiment, R^1, R^2 and R^3 are each selected from amino, hydrogen, halogen, hydroxy, nitro, C_{1-8} alkyl, C_{1-8} alkoxy C_{1-8} alkylthio, C_{1-4} alkylamino, or R^1 and R^2 or R^1 and R^3 together form an optionally substituted methylenedioxy or ethylenedioxy group; $R^{3'}$ is hydrogen; R^4 is hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, di-[C_{1-4} alkyl]amino, nitro or trifluoromethyl;
R^5 is hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;
Z is absent or represents CH_2, oxygen, $S(O)_m$, wherein m is 0, 1 or 2, or NR^b wherein R^b is hydrogen or R^b is C_{1-4} alkyl, and
R^7 is an optionally substituted phenyl, benzyl, pyridyl, dioxolanyl, phenoxy, benzyloxy, phenylamino, benzylamino, phenymercapto or benzylmercapto group, preferably a phenyl, fluorophenyl, pyridyl, 1,3-dioxolanyl or benzyl group.

When the group Z is absent, $R^6 = R^7$.

In a further embodiment, R^1, R^2 and R^3 are each selected from hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy or an adjacent pair together form a methylenedioxy or ethylenedioxy group; and $R^{3'}$ is hydrogen.

In a further embodiment, R^6 is in the ring which is remote from Y when U represents a bicyclic group.

In a further embodiment, X is N.

In a further embodiment, Y is NR^b, $NR^b(CH_2)$, or $(CH_2)NR^b$, preferably Y is NR^b.

Heterocyclic groups comprise one or more rings which may be saturated, unsaturated or aromatic and which may independently contain one or more heteroatoms in each ring.

Carbocyclic groups comprise one or more rings which may be independently saturated, unsaturated or aromatic and which contain only carbon and hydrogen.

Suitably X is nitrogen.
Suitably Y is a group NR wherein R is hydrogen or methyl, preferably hydrogen.
Suitably R^1 and R^2 are independently hydrogen; C_{1-4} alkyl, such as methyl; or C_{1-4} alkoxy, such as methoxy.
Suitably R^3 and $R^{3'}$ are independently hydrogen, methyl or methoxy.
Suitably R^4 is hydrogen, halogen or methyl, preferably R^4 is hydrogen.
Suitably R^5 is hydrogen or methyl.
Suitably R^6 is phenyl, fluorophenyl, phenethyl, benzyl, pyridyl, phenylsulphonyl, benzylsulphonyl, phenoxy, benzyloxy or 1,3-dioxolanyl.

One or both of the rings comprising the mono or bicyclic ring system may be aromatic or non-aromatic. The R^4 and R^6 groups may be bound to the ring system by either a carbon atom or a heteroatom of the ring system. The ring system itself may be bound to the bridging group Y which is linked to the 4-position of the quinoline or quinazoline skeleton by a carbon atom or a heteroatom. The R^4 and R^6 groups may be bound to either ring when U represents a bicyclic ring system, but these groups are preferably bound to the ring which is not bound to the bridging group Y in such a case.

Examples of suitable mono or bicyclic groups U which are ultimately linked to the 4-position of the quinoline or quinazoline include: isoindenyl, indenyl, indanyl, naphthyl, 1,2-dihydronaphthyl or 1,2,3,4-tetrahydronaphthyl, pyrrolyl, pyridinyl,

pyridazinyl, pyrimidinyl, pyrazinyl, furanyl, 2H-pyranyl, thiophenyl, 1H-azepinyl, oxepinyl, thiepinyl, azocinyl, 2H-oxocinyl, thieno[2,3-b] furanyl, thianaphthenyl, indolyl, indolinyl, isioindolyl, isoindolinyl, indolizinyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl, 1H-indazolyl; 2,3-dihydro-1H-indazolyl, benzoxazolyl, 2,3-dihydrobenzoxazolyl, benzo[c]isoxazolyl, benzo[d]isoxazolyl, 2,3-dihydrobenzo[d]isoxazolyl, benzothiazoyl, 2,3-dihydrobenzothiazolyl, benzo[c]isothiazolyl, benzo[d]isothiazolyl, 2,3-dihydrobenzo[d]isothiazoly, 1H-benzotriazolyl, benzo[c]furanyl, benzo[c][1,2,3]thiadiazolyl, benzo[d][1,2,3]oxadiazolyl, benzo[d][1,2,3]thiadiazolyl, quinolyl, 1,2-dihydroquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolyl 1,2,3,4-tetrahydroisoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 4H-1, 4-benzoxazinyl, 2,3-dihydro-4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl or 2,3-dihydro-4H-1,4-benzothiazinyl.

Suitably U represents an indolyl, isoindolyl, indolinyl, isoindolinyl, lH-indazolyl, 2,3-dihydro-lH-indazolyl, lH-benzimidazolyl, 2,3-dihydro-lH-benzimidazolyl or lH-benzotriazolyl group.

Suitably the 5, 6, 7, 8, 9 or 10-membered heterocyclic moiety is selected from the group comprising: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazoline, oxazolidine, thiazole, thiadiazole, benzofuran, indole, isoindole, quinazoline, quinoline and isoquinoline.

Suitably the the 5, 6, 7, 8, 9 or 10-membered carbocyclic moiety is selected from the group comprising: phenyl, benzyl, indene, naphthalene, tetralin, decalin, cyclopentyl, cyclohexyl and cycloheptyl.

By halo is meant fluoro, chloro, bromo or iodo.

Alkyl groups containing three or more carbon atoms may be straight, branched or cyclised.

In an embodiment, the optional substitutents for the carbocyclic or heterocyclic moiety, which may be present at any available position of said moiety, are selected from the group comprising:

$(CH_2)_qS(O)_m$-C_{1-4}alkyl, $(CH_2)_qS(O)_m$-C_{3-6}cycloalkyl, $(CH_2)_qSO_2NR^8R^9$, $(CH_2)_qNR^8R^9$, $(CH_2)_qCO_2R^8$, $(CH_2)_qOR^8$, $(CH_2)_qCONR^8R^9$, $(CH_2)_qNR^8COR^9$, $(CH_2)_qCOR^8$, $(CH_2)_qR^8$, $NR^8SO_2R^9$ and $S(O)_mR^8$,

wherein q is an integer from 0 to 4 inclusive; m is 0,1 or 2;
R^8 and R^9 are independently selected from the group comprising hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, a 5- or 6-membered saturated or unsaturated heterocyclic ring which may be the same or different and which contains one or more heteroatoms which are selected from N, O or S, with the proviso that the heterocyclic ring does not contain two adjacent O or S atoms.

In a further embodiment the optional substitutents for the carbocyclic or heterocyclic moiety are selected from the group comprising morpholine, piperazine, piperidine, pyrrolidine, tetrahydrofuran, dioxolane, oxothiolane and oxides thereof, dithiolane and oxides thereof, dioxane, pyridine, pyrimidine, pyrazine, pyridazine, furan, thiofuran, pyrrole, triazine, imidazole, triazole, tetrazole, pyrazole, oxazole, oxadiazole and thiadiazole.

Other optional substituents for the carbocyclic or heterocyclic moiety and also for other optionally substituted groups include, but are not limited to, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, carboxylate and C_{1-4} alkoxy carboxyl.

Preferred compounds of the present invention include:

4-(1-benzyl-5-indolylamino)quinazoline;
4-(1-benzyl-5-indolylamino)-6,7-dimethoxyquinazoline;
4-(2-benzyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
4-(2-benzyl-5-benzimidazolylamino)-quinazoline;

4-(2-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indazolylamino)-quinazoline;
4-(1-phenylsulphonyl-5-indolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-2,3-dihydroindolyl-5-amino)-6,7-dimethoxyquinazoline;
4- [3-(4-fluorophenyl)-6-indazolylamino]-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indolylamino)-6,7-diethoxyquinazoline;
4-[1-[2-(1,3-dioxolan-2-yl)-ethyl]-5-indazolylamino]-6,7-dimethoxyquinazoline;
4-(1-benzyl-6-indolyamino)-6,7-dimethoxyquinazoline;
4-(2-phenyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indolylamino)-6,7-methylenedioxyquinazoline;
4-(3-benzyl-5-benzimidazolylamino)-quinazoline;
4-(1-benzyl-5-benzimidazolylamino)-quinazoline;
4-(2-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(3-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(2-phenethyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-phenethyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(2-(2-pyridyl)-5-benzimidazolylamino)-quinazoline;
4-(2-benzylsulphonyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
and salts thereof, particularly pharmaceutically acceptable salts thereof.

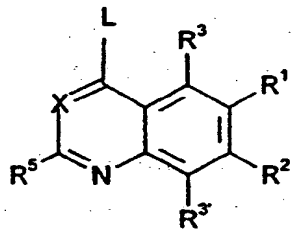
Particularly preferred compounds of the present invention include:
4-(2-benzyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
4-(2-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indazolylamino)-quinazoline;
4-(1-phenylsulphonyl-5-indolylamino)-6,7-dimethoxyquinazoline;
and salts thereof, particularly pharmaceutically acceptable salts thereof.

Certain compounds of the formula (I) contain asymmetric carbon atoms and are, therefore, capable of existing as optical isomers. The individual isomers and mixtures of these are included within the scope of the present invention. Likewise,

it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen in the compound of formula (I). The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance although for therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycollic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids.

In a further aspect, the present invention provides a process for the preparation of a compound of the formula (I), which process comprises the reaction of a compound of the formula (II).



(II)

with a compound of the formula III :

UYH (III)

wherein L is a leaving group and U, X, Y and R^1 to R^6 are as hereinbefore defined. Suitable leaving groups will be well known to those skilled in the art and include, for example, halo and sulphonyloxy groups such as chloro, bromo, methanesulphonyloxy and toluene-p-sulphonyloxy.

The reaction is conveniently carried out in the presence of a suitable inert solvent, for example a C_{1-4} alkanol, such as isopropanol, a halogenated hydrocarbon, an ether, an aromatic hydrocarbon or a dipolar aprotic solvent, such as acetone, at a non-extreme temperature, for example from 0 to 150°, suitably 10 to 100°C, preferably 50 to 100°C.

Optionally, the reaction is carried out in the presence of a base, for example an organic amine such as triethylamine, or an alkaline earth metal carbonate, hydride or hydroxide, such as sodium or potassium carbonate, hydride or hydroxide.

The compound of the formula (I) may be obtained from this process in the form of a salt with the acid HL, wherein L is as hereinbefore defined, or as the free base by treating the salt with a base as hereinbefore defined.

The preparation of compounds (II) and (III) is well known to those skilled in the art.

In addition to the above, one compound of formula (I) may be converted to another compound of formula (I) by chemical transformation of the appropriate substituent or substituents using appropriate chemical methods (see, for example, J. March "Advanced Organic Chemistry", Edition III, Wiley Interscience, 1985).

For example, a compound containing an alkyl or aryl mercapto group may be oxidised to the corresponding sulphinyl or sulphonyl compound by use of an organic peroxide (eg benzoyl peroxide) or suitable inorganic oxidant (eg OXONE ®)

A compound containing a nitro substituent may be reduced to the corresponding amino-compound, eg by use of hydrogen and an appropriate catalyst (if there are no other susceptible groups) or by use of Raney Nickel and hydrazine hydrate.

Amino or hydroxy substituents may be acylated by use of an acid chloride or an anhydride under appropriate conditions. Equally an acetate or amide group may

be cleaved to the hydroxy or amino compound respectively by treatment with, for example dilute aqueous base.

In addition reaction of an amino substituent with triphosgene and another amine (eg aqueous ammonia, dimethylamine) gives the urea substituted product.

An amino substituent may also be converted to a dimethylamino substituent by reaction with formic acid and sodium cyanoborohydride.

The present invention also provides compounds of formula (I) and pharmaceutically acceptable salts thereof (hereinafter identified as the 'active ingredients') for use in medical therapy, and particularly in the treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds are especially useful for the treatment of disorders caused by aberrant c-erbB-2 activity such as breast, ovarian, non-small cell lung, pancreatic, gastric and colon cancers.

A further aspect of the invention provides a method of treatment of the human or animal body suffering from a disorder mediated by aberrant protein tyrosine kinase activity which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to the human or animal patient.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for th treatment of malignant tumours.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of atherosclerosis, restenosis or thrombosis.

A further aspect of the present invention provides a pharmaceutical formulation comprising one or more compounds of formula (I), or pharmaceutically acceptable salt(s) thereof, together with one or more pharmaceutically acceptable carriers.

Whilst it is possible for the compounds or salts of the present invention to be administered as the new chemical, it is preferred to present them in the form of a pharmaceutical formulation.

According to a further feature of the present invention we provide pharmaceutical formulations comprising at least one compound of the formula (I) or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain for example 0.5mg to 1g, preferably 5mg to 100mg of a compound of the formula (I) depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the activ ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or

suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as en mas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e.

by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and salts of the formula (I) have anticancer activity as demonstrated hereinafter by their inhibition of the protein tyrosine kinase c-erbB-2

enzyme. It has thus been established that compounds of the present invention are of use in medicine and, in particular in the treatment of certain human malignancies, for example breast, ovarian non-small cell lung, pancreatic, gastric and colon cancers. Accordingly, the present invention provides a method for the treatment of susceptible malignancies in an animal, e.g. a human, which comprises administering to the animal a therapeutically effective amount of a compound or salt of the present invention. In the alternative, there is also provided a compound or salt of the present invention for use in medicine and, in particular, for use in the treatment of cancers.

The present invention also provides the use of a compound of formula (I) or a salt thereof for the manufacture of a medicament for treatment of malignant tumours.

The animal requiring treatment with a compound or salt of the present invention is usually a mammal, such as a human being.

A therapeutically effective amount of a compound or salt of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant phsician or veterinarian. However, an effective amount of a compound of the present invention for the treatment of neoplastic growth, for example colon or breast carcinoma will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An eff ctive amount of a salt of the present invention may be determined as a proportion of the effective amount of the compound per se.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

IR spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer or a Bruker FS66 spectrophotometer.
1H NMR spectra were obtained on a Bruker WM 360-NMR spectrophotometer at 360MHz, or on a Bruker AC200 spectrophotometer at 200 MHz. J values are given in Hz.
Mass spectra were obtained on Varian CH5D (EI), Kratos Concept (EI) or Kratos Ms50 (FAB) machines.
Analytical thin layer chromatography (TLC) was used to verify the purity of some intermediates which could not be isolated for full characterisation, and to follow the progess of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254).
Unless otherwise stated, column chromatography for the purification of some compounds, used Merck Silica Gel 60 (Art. 1.09385, 230-400 mesh), and the stated solvent system under pressure.
Petrol refers to petroleum ether, either the fraction boiling at 40-60°C, or at 60-80°C.
Ether refers to diethyl ether.
THF refers to tetrahydrofuran.
DMF refers to dimethylformamide.
DCM refers to dichloromethane.
DMSO refers to dimethylsulphoxide.

Preparation Of Intermediates

4-Chloroquinazoline was prepared from 4-hydroxyquinazoline (commercially available) according to the published method (J. Org. Chem, 27, 958 (1962)).

4-Chloro-6,7-dimethoxyquinazoline was prepared in an analogous manner according to the proceedure described in European Patent Application 566 226 A1 (Zeneca Limited).

5-Amino-1-benzyl-2,3-dihydroindole was prepared according to the published method (Chem. Ber., 102, 1084-5, (1969)).

5-Amino-2-(2-pyridyl)-benzimidazole was prepared according to the published method (J. Med. Chem., 22, 1113-8, (1979)).

5-Amino-2-benzylbenzimidazole was prepared according to the published method (J. Het. Chem., 23, 1109-13, (1986)).

5-Amino-1-benzylbenzimidazole was prepared according to the published method (Khim. Geterotsikl. Soedin, 7, 1136-8, (1971)).

5-Amino-1-benzylindazole was prepared according to the published method (FR 5600 68.01.08).

5-Amino-2-phenylbenzimidazole was prepared according to the published method (J. Org. Chem., 60, 5678-82, (1995).

5-Amino-1-phenylsulphonylindole was prepared according to the published method (J. Org. Chem., 55, 1379-90, (1990)).

2-Fluoro-4-nitrobenzoyl chloride was prepared according to the published method (J. Med. Chem., 37, 2361-70, (1994)).

1-Benzyl-5-nitroindole

Dry dimethylsulphoxide (20 ml) was added to potassium hydroxide (4.2 g, 0.074 mol) (crushed pellets) and the mixture was stirred under nitrogen for 5 mins. 5-Nitroindole (commercially available) (3.0 g, 0.019 mol) was then added and the red mixture stirred for 30 min at r.t. The mixture was then

cooled to -10 °C, benzyl bromide (4.4 ml, 0.037 mol) was slowly added and the mixture stirred and allowed to warm to r.t.. over a period of 40 mins. Water (50 ml) was then added and the mixture was extracted with diethyl ether (2 x 200 ml). The extracts were washed with water (4 x 50 ml), dried over sodium sulphate and evaporated to leave an oily solid. The excess benzyl bromide was removed by dissolving the whole in diethyl ether (50 ml), diluting this solution with 40-60 petrol (50 ml) and then gradually removing the diethyl ether *in vacuo* to leave a yellow solid suspended in the petrol. The solid was filtered, washed with copious amounts of 40-60 petrol and dried to give 1-benzyl-5-nitroindole (2.4 g, 51%) as a yellow solid, m.p. 102-104 °C; δH [$^2H_6$]-DMSO 8.53 (1H, s, 4-H), 8.00 (1H, d, J 9, 6-H), 7.78 (1H, s, 2-H), 7.68 (1H, d, J 9, 7-H), 7.36-7.20 (5H, m, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 6.81 (1H, s, 3-H), 5.52 (2H, s, CH_2).

5-Amino-1-benzylindole

A solution of 1-benzyl-5-nitroindole (0.51 g, 0.02 mol) in a mixture of ethyl acetate (25 ml) and methanol (25 ml) was carefully added to 10% palladium on charcoal (45 mg). The resulting suspension was stirred at room temperature under one atmosphere of hydrogen. When the reaction was complete (indicated by tlc or calculated uptake of hydrogen) the suspension was filtered through a pad of hyflo, and the filtrate evaporated to dryness to give 5-amino-1-benzylindole (0.40 g, 91%) as an off-white solid, m.p. 66-68 °C: δH [$^2H_6$]-DMSO 7.30-7.12 (6H, m, 2-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 7.08 (1H, d, J 8, 7-H), 6.70 (1H, s, 4-H), 6.49 (1H, d, J 8, 6-H), 6.18 (1H, s, 3-H), 5.28 (2H, s, CH_2), 4.38 (2H, br s, NH_2).

5-Nitro-3-benzylbenzimidazole and 6-nitro-3-benzyl-benzimidazole

5-nitrobenzimidazole (1 g, 6.13 mmol) in acetone (20 ml) containing potassium hydroxide pellets (1 g, 18.39 mmol) was stirred and treated with benzyl bromide (0.73 ml, 6.13 mmol). After 1h the mixture was acidified to ca pH 7, diluted with water, and extracted with ethyl acetate. The dried extracts were vaporated giving a cream solid (1.56g, 100 %); m/z $(M + 1)^+$ 254.

5-Amino-3-benzylbenzimidazole

A mixture of 5-nitro-3-benzylbenzimidazole and 6-nitro-3-benzylbenzimidazole (0.25 g, 0.987 mmol) in ethyl acetate was hydrogenated over palladium catalyst (50% w/w H_2O, 10% in carbon, 0.1 g) at room temperature and pressure. (Hydrogen uptake = 81ml, theoretical = 71ml). The mixture was filtered through Celite and the filtrate evaporated. The residue was chromatographed on silica gel (Merck 9385, 30 g). Elution with CH_2Cl_2 :EtOH:NH_3 100:8:1 gave the desired isomer (determined by nuclear Overhauser effect nmr) as a colourless solid (0.083 g, 38%); m/z $(M + 1^+)$ 224.

1-Benzyl-5-nitroindazole and 2-Benzyl-5-nitroindazole

5-nitroindazole (0.5 g, 3.065 mmol) in acetone (10 ml) containing potassium hydroxide pellets (0.51 g, 9.090 mmol) was stirred and treated dropwise with benzylbromide (0.37 ml, 3.065 mmol). The mixture was stirred for 3h and then acidified with 2N, HCl and was extracted with ethylacetate. The dried organic phase was evaporated giving a brown solid (0.78 g, 100%); nmr shows isomeric mixture; m/z $(M + 1)^+$ 254.

5-Amino-1-benzylindazole and 5-Amino-2-benzylindazole

The isomeric mixture of nitroindazoles (0.4 g, 1.579 mmol) was hydrogenated in ethanol (35 ml) over palladium catalyst (10% on carbon, 0.1 g) at room temperature and pressure. Hydrogen uptake = 120 ml (theory =114 ml), reaction time 45 mins. The catalyst was removed by filtration through Celite and the solvent evaporated giving a yellow solid (0.32 g 91%); m/z $(M + 1)^+$ 224.

Mixture of 1-, 2- and 3-Benzyl-5-aminobenzotriazole

An isomeric mixture of 1-, 2- and 3-benzyl-5-nitrobenzotriazole (0.518 g, 2.037 mmol) in THF (15 ml) was hydrogenated over platinum catalyst (5% on carbon, 0.1 g) at room temperature and pressure. Hydrog n uptake = 145 ml (theoretical uptake = 147 ml); r action time = 4h. The catalyst was removed by filtration through celite and the solvent then evaporated giving a pale yellow oil (0.456 g, 100%); m/z $(M + 1)^+$ 225.

Mixture of 1-, 2-, and 3-Benzyl-5-nitrobenzotriazole

5-nitrobenzotriazole (0.750 g, 4.569 mmol) and benzylbromide (0.54 ml, 4.569 mmol) in acetone (30 ml) containing potassium carbonate (1.89 g, 13.675 mmol) was stirred and was heated to reflux for 2h. After this time the solvent was evaporated, and then the residue partioned between water and ethyl acetate. The dried extracts were evaporated giving an orange oil which solidified on standing (1.15 g, 100%); m/z $(M + H)^+$ 255

2, 4'-Difluoro-4-nitrobenzophenone

A stirred solution of 2-fluoro-4-nitrobenzoyl chloride (2.91 g, 12.97 mmol) in fluorobenzene (10 ml) was treated with anhydrous aluminium chloride (1.73 g, 12.97 mmol). After 2h the mixture was poured into cold ((0°C) 2N hydrochloric acid, and the product extracted with ethylacetate. The combined extracts were washed with water, dried, and evaporated giving a pale brown oil which crystallised on standing (3.35 g, 98%); δH ($CDCl_3$) 8.17 (IH,dd), 8.07 (IH,dd), 7.85 (2H, m), 7.71 (IH,dd), 7.19 (2H, m).

6-Amino-3-(4-fluorophenyl)-indazole

A mixture of 2,4'-difluoro-4-nitrobenzophenone (0.263 g,1 mmol) and hydrazine hydrate (0.2 ml, 4 mmol) in ethanol (8 ml) was heated to re flux for 4 days. The solvent was then evaporated and the residue chromatographed on silica gel (Merck 9385, 30 g). Elution with $CH_2 Cl_2$: EtOH:NH_3 200:8:1 gave a colourless solid (0.075 g, 33 %); m/z $(M + 1)^+$ 228

1-[2-(1,3-Dioxolan-2-yl)-ethyl)-5-nitroindazole

5-nitroindazole (0.5 g, 3.065 mmol) potassium carbonate (1.06 g, 7.66 mmol) and bromomethyldioxolane (0.33 ml, 3.218 mmol) in acetonitrile (20 ml) was stirred and heated to reflux for 18h. The cooled mixture was partitioned b tween water and ethylacetate. The dried extracts were vaporated giving a yellow solid. This material was chromagraphed on silica gel (Merck 9385, 40 g). Elution with ethylacetate:cyclohexane 1:1 gave a colourless solid (0.411 g, 57 %); m/z $(M + 1)^+$ 250.

5-Amino-1-[2-(1,3-dioxolan-2-yl)-ethyl]-indazole

1-[2-(1,3-Dioxolan-2-yl)-ethyl]-5-nitroindazole (0.405 g, 1.625 mmol) in THF (15 ml) was hydrogenated over platinum (5% on carbon, 0.05 g) at room temperature and pressure. Hydrogen uptake = 140 ml, theoretical = 117 ml. Reaction Time = 1.5h. The catalyst was removed by filtration through celite and the filtrate was evaporated giving a pale yellow solid (0.355 g, 100%); m/z $(M + 1)^+$ 220.

Mixture of 1- and 2-Phenethyl-5-nitroindazole

A mixture of 5-nitroindazole (0.500 g, 3.065 mmol) phenethylbromide (0.42 ml, 3.065 mmol) and potassium carbonate (1.06 g, 7.670 mmol) in acetonitrile (20 ml) was stirred and heated to reflux for 18h. The cooled mixture was partioned between water and ethylacetate. The dried extracts were evaporated giving a yellow solid (0.810 g, 99%); m/z $(M + 1)^+$ 268.

Mixture of 1- and 2-Phenethyl-5-aminoindazole

An isomeric mixture of 1- and 2-phenethyl-5-nitroindazole (0.800 g, 2.993 mmol) in THF (25 ml) was hydrogenated over palladium (50% w/w. H_20, 10% on carbon, 0.2 g) at room temperature and pressure. Hydrogen uptake = 232 ml; theoretical uptake = 215 ml. The catalyst was removed by filtration through celite and then the filtrate evaporated giving a yellow-green oil (0.690 g, 97%); m/z $(M + 1)^+$ 238.

2- Benzylthio-5-nitrobenzimidazole

2-Mercapto-5-nitrobenzimidazole (0.25 g, 1.280 mmol), benzyl bromide (0.15 ml, 1.280 mmol) and potassium carbonate (0.531 g, 3.840 mmol) in acetone (10 ml) was heated to reflux for 2h. The cooled mixture was partitioned between water and ethylacetate. The dried extracts were evaporated giving a pale yellow solid (0.365 g, 100%); m/z $(M + 1)^+$ 286.

2-Benzylsulphonyl-5-nitrobenzimidazole

1-Benzylthio-5-nitrobenzimidazole (0.36g, 1.261mmol) and oxon (2.32g, 3.783 mmol) in aqueous methanol (1:3; 20 ml) was stirred at 20°C for 18 hr. The methanol was then evaporated and the residue partitioned between water and

dichloromethane. The dried extracts were then evaporated giving a yellow foam (0.384g, 96%); m/z $(M + 1)^+$ 318

5-Amino-2-benzylsulphonylbenzimidazole

2-Benzylsulphonyl-5-nitrobenzimidazole (0.165g, 0.520mmol) in ethanol (10 ml) was hydrogenated over palladium catalyst (50% w/w H_20, 10% on carbon, 0.1g) at room temperature and pressure. Hydrogen uptake = 57 ml, theoretical = 57 ml; reaction time = 3 hr. The catalyst was removed by filtration through Celite and the filtrate evaporated giving a colourless oil (0.146 mg, 98%); m/z $(M + 1)^+$ 288.

General Procedure

The optionally substituted quinazoline or quinoline and the specified amine were mixed in an appropriate solvent and heated to reflux. When the reaction was complete (as judged by TLC), the reaction mixture was allowed to cool. The resulting suspension was diluted with acetone and the solid collected by filtration, washing with excess acetone, and dried at 60°C *in vacuo*.

Example 1

4-(1-Benzyl-5-indolylamino)quinazoline hydrochloride

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 5-amino-1-benzylindole (0.16 g, 0.73 mmol) were reacted in 2-propanol (10 ml) for 30 minutes according to the General Procedure. The bright yellow solid thus obtained was 4-(1-benzyl-5-indoylamino)quinazoline hydrochloride (0.22 g, 92%), m.p. 265-266 °C; (Found: C, 70.64; H, 4.83, N, 14.11. $C_{23}H_{18}N_4$ HCl.0.2H_2O requires: C, 70.75; H, 5.01; N, 14.35%); δH [$^2H_6$]-DMSO 11.70 (1H, br s, NH), 8.90 (1H, d, J 9, 8-H), 8.80 (1H, s, 2-H), 8.10 (1H, t, J 8, 6-H), 7.98 (1H, d, J 8, 5-H), 7.87 (1H, s, 4'-H), 7.83 (1H, t, J 8, 7-H), 7.60 (1H, s, 2'-H), 7.55 (1H, d, J 9, 6'-H), 7.40-7.20 (6H, m, 7'-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 6.57 (1H, s, 3'-H), 5.48 (2H, s, CH_2); m/z (%) 351 (100, M+1+); ν_{max} (KBr disc)/cm-1 2592, 1626, 1610, 1566, 1485, 1423, 1371.

Example 2

4-(1-Benzyl-5-indolylamino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.10 g, 0.45 mmol) and 5-amino-1-benzylindole (0.37 g, 0.63 mmol) were reacted in 2-propanol (15 ml) for 4 h according to the General Procedure. The pale yellow solid thus obtained was 4-(1-benzyl-5-indoylamino)-6,7-dimethoxyquinazoline hydrochloride (0.16 g, 78%), m.p. 244-245 °C; (Found: C, 66.66; H, 4.97 N, 12.40. $C_{25}H_{22}N_4O_2.HCl.0.2\ H_2O$ requires: C, 66.64; H, 5.24; N, 12.43%); δH [$^2H_6$]-DMSO 11.42 (1H, br s, NH), 8.68 (1H, s, 2-H), 8.32 (1H, s, 8-H), 7.80 (1H, s, 4'-H), 7.59 (2H, s, 2'-H), 7.53 (1H, d, J 9, 6'-H), 7.40-7.20 (7H, m, 5-H, 7'-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 6.53 (1H, s, 3'-H), 5.48 (2H, s, CH_2), 4.00 (6H, 2 x s, 2 x OCH_3); m/z (%) 411 (100, M+1$^+$); ν_{max} (KBr disc)/cm^{-1} 2837, 1632, 1576, 1568, 1512, 1454, 1437, 1365, 1281.

Comparative
4-(5-Indolylamino)quinazoline hydrochloride
This was synthesized for comparative purposes in an analogous manner to Example 1 using 5-aminoindole.

Comparative Example 4
4-(5-Indolylamino)-6,7-dimethoxyquinazoline hydrochloride
This was synthesized for comparative purposes in an analogous manner to Example 2 using 5-aminoindole.

Example 5
4-(2-Benzyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6, 7-dimethoxyquinazoline (0.112 g, 0.5 mmol) and 5-amino-2-benzylbenzimidazole (0.111 g, 0.5 mmol) were reacted in acetonitrile (10 ml) according the General Procedure. The desired compound was collected by filtration as a cream solid (0.144 g, 65%); m/z $(M+1)^+$ 412; δH (d_6-DMSO) 8.48 (IH,s), 8.51 (IH, s), 8.19 (IH,s), 7.85 (2H,s), 7.35-7.52 (6H, m), 4.54 (2H,s), 4.02 (6H, 2 x s).

Example 6

4-(2-Benzyl-5-benzimidazolylamino)-quinazoline hydrochloride

4-Chloroquinazoline (0.147g, 0.895mmol) and 5-amino-2-benzylbenzimidazole (0.200g, 0.895mmol) were reacted together in 2-propanol (10 ml) according to the General Procedure. The desired material was collected by filtration as a pale yellow solid (0.241g, 69%); m/z (M + 1^+) 352; δH (d_6-DMSO) 8.9-9.1 (2H, s + d), 8.2 (IH,s), 7.7-8.15 (5H, m), 7.3-7.5 (5H,m), 4.6 (2H,s).

Example 7
4-(2-Benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.206 g, 0.918 mmol) and an isomeric mixture of 5-amino-2-benzylindazole and 5-amino-1-benzylindazole (0.205 g, 0.918 mmol) was reacted in acetonitrile (10ml) according to the General Procedure. On cooling a yellow precipitate was formed, which was collected by filtration. This material was chromatographed on silica gel (Merck 9385, 35 g). Elution with CH_2Cl_2:EtOH:NH_3 200:8:1 gave a beige crystalline solid (0.104 g, 27%); m/z (M + 1)$^+$ 412; δH (d_6-DMSO) 8.65 (IH, s), 8.09 (IH,d), 7.89 (IH,s), 7.76 (1H,d), 7.24-7.40 (7H,m), 7.06 (IH,s), 5.60 (2H,s), 4.02 (6H, 2 x s).

Also isolated from this chromatography column was 4-(1-benzyl-5-imidazolylamino)-6,7-dimethoxyquinazoline (0.072 g, 19%) as a colourless solid; LC/MS - single isomer (M + 1)$^+$ 412; δH (d_6-DMSO) 8.62 (IH, s), 8.00 (IH,d), 7.53 (IH, dd), 7.2-7.4 (7H,m), 7.03 (IH,s), 5.61 (2H,s), 4.02 (6H, 2 x s), 4.02 (6H, 2 x s) .

The isomers were assigned by means of the nuclear Overhauser effect.

Example 8
4-(1-Benzyl-5-indazolylamino)-quinazoline hydrochloride

4-Chloroquinazoline (0.08 g, 0.488 mmol) and 5-amino-1- benzylindazole (0.109 g, 0.488 mmol) were reacted in acetonitrile (10 ml) according to General Procedure. The desired compound was collected by filtration as a pale yellow

solid (0.14 g, 74%); m/z $(M + 1)^+$ 352; δH (d_6-DMSO) 8.88-8.92 (2H,m), 8.21 (IH,s), 7.8-8.15 (5H, m), 7.64 (IH, dd), 7.2-7.35 (5H,m), 5.72 (2H,s).

Example 9

4-(1-Phenylsulphonyl-5-indolylamino)-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.132 g, 0.587 mmol) and 5-amino-1-phenylsulphonylindole (0.160 g, 0587 mmol) were reacted in acetonitrile(15 ml) according to the General Procedure. On cooling a yellow solid was formed which was collected by filtration, and then chromatographed on silca gel (Merck 9385, 30 g). Elution with CH_2Cl_2 : EtOH:NH_3 200:8:1 gave a colourless solid (0.146 g, 54%); m/z $(M + 1)^+$ 461; δH ($CDCl_3$) 8.61 (IH,s), 7. 8-8.0 (3H, m), 7.4-7.65 (4H, m), 7.2-7.3 (3H, m), 7.03 (IH,s), 6.68 (1H,d), 4.02 (6H 2 x s).

Example 10

4-(1-Benzyl -2,3-dihydroindol-5-amino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.158 g, 0.703 mmol) and 5-amino-1-benzyl-2,3-dihydroindole (0.158 g, 0.703 mmol) were reacted in 2-propanol (10 ml) according to the General Procedure. The desired product was obtained by filtration as a yellow solid (0.264 g, 84%); m/z $(M+1^+)$ 413; δH (d_6-DMSO) 8.75 (IH,s), 8.20 (IH,s), 7.20-7.40 (8H,m), 6.65 (IH,d), 4.35 (2H,s), 3.97 (6H,s), 3.34 (2H,t), 2.97 (2H,t).

Example 11

4- [3-(4-Fluorophenyl)-6-indazolylamino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.064 g, 0.286 mmol) and 6-amino-3-(4-fluorophenyl)-indazole (0.065 g, 0.286 mmol) were reacted in acetonitrile (5 ml) according to the General Procedure. The desired compound was collected by filtration as a beige solid (0.115 g, 89%); m/z $(M + 1)^+$ 416; δH (d_6-DMSO) 8.88

(IH,s), 8.34 (IH,s), 8.03-8.20 (4H,m), 7.53 (IH,dd), 7.23-7.41 (3H,m), 4.02 (6H, 2 x s).

Example 12

4-(1-Benzyl-5-indolylamino)-6,7-diethoxyquinazoline hydrochloride

Prepared from 4-Chloro-6,7-diethoxyquinazoline and 5-amino-1-benzylindole by an analogous method to Example 2. M.pt. 251-258°C; Analysis found C, 67.64; H, 5.19; N, 11.69; $C_{27}H_{26}N_4O_2HCl$ requires C, 67.92; H, 5.75, N, 11.67%.

Example 13

4-[1-[2-(1,3-Dioxolan-2-yl)-ethyl]-5-indazolylamino]-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.358 g, 1.596 mmol) and 5-amino-1-[2-(1,3 - dioxolan-2-yl)ethyl]indazole (0.350 g, 1.596 mmol) were reacted in acetonitrile(20 ml) according to the General Procedure. On cooling a yellow precipitate was formed which was collected by filtration. This material was chromatographed on silica gel (Merck 9385, 40 g). Elution with CH_2Cl_2 : EtOH:NH_3 100:8:1 gave an off-white foam (0.486 g, 75%); LC/MS - single isomer with $(M + 1)^+$ 408; δH ($CDCl_3$) 8.63 (IH,s), 8.02 (IH,s), 7.99 (IH,s), 7.57 (2 H,s), 7.28 (IH,s), 7.06 (IH,s), 5.31 (IH, t), 4.58 (2H,d), 4.02 (6H, 2 x s), 3.85 (4H,s).

Example 14

4-(1-Benzyl-6-indolylamino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.031 g, 0.19 mmol) and 6-amino-1-benzylindole (0.05 g, 0.23 mmol) were reacted in 2-propanol (6.5 ml) for 30 min according to the General procedure. the light orange solid thus obtained was 4-(1-benzyl-6-indolylamino)-6,7-dimethoxyquinazoline hydrochloride (0.045 g, 62%); M.pt. 241-242°C; Analysis found C, 66.97; H, 5.19; N, 12.34; $C_{25}H_{22}N_4O_2HCl$ requires C, 67.18; H, 5.19; N, 12.53%; δH (d^6-DMSO) 11.15 (1H, br s, NH), 8.68 (1H, s, 2-H), 8.14 (1H, s, 8-H), 7.72 (1H, s, 7'-H), 7.64 (1H, d, J 9, 4'-H), 7.58 (1H, s, 2'-H), 7.35-7.20 (9H, m, 5-H, 5'-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 6.56 (1H, s, 3'-

H), 5.42 (2H, s, CH_2), 3.99 (6H, 2 x s, 2 x OCH_3); m/z (%) 411 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 2623, 1634, 1578.

Example 15
4-(2-Phenyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6, 7-dimethoxyquinazoline (0.18 g, 0.803 mmol) and 5-amino-2 phenylbenzimidazole (0.168 g, 0.803 mmol) were reacted in acetonitrile (10 ml) according to the General Procedure. The desired compound was collected by filtration as a beige solid (0.295g, 85%); m/z $(M + 1)^+$ 398; δH (d_6-DMSO) 8.79 (1 H,s), 8.2-8.3 (3H, m), 8.02 (I H, s), 7.73 (I H,d), 7.5-7.65 (4H, m), 7.32 (IH ,s), 4.01 (6H, 2 x s).

Example 16
4-(1-Benzyl-5-indolylamino)-6,7-methylenedioxyquinazoline hydrochloride
Prepared from 4-Chloro-6,7-methylenedioxyquinazoline and 5-amino-1-benzylindole by an analogous method to Example 2. M.pt. 282-284°C; Analysis found C, 66.13; H, 4.28; N, 12.86; $C_{24}H_{18}N_4O_2HCl$ requires C, 66.19; H, 4.40, N, 12.86%.

Example 17
4-(3-Benzyl-5-benzimidazolylamino)-quinazoline hydrochloride
4-Chloroquinazoline (0.053 g, 0.322 mmol) and 5-amino-3-benzylbenzimidazole (0.72 g, 0.322 mmol) were reacted in 2-propanol (5 ml) according to the General Procedure. The desired compound was obtained by filtration as a pale yellow solid (0.05 g, 40%); m/z $(M + 1^+)$ 352; δH (d_6 DMSO) 9.35 (IH, s), 8.9 (2H, m), 7.5- 8.2 (6H,m), 7.3-7.5 (5H,m), 5.65 (2H,s).

Example 18
4-(1-Benzyl-5-benzimidazolylamino)-quinazoline hydrochloride

4-Chloroquinazoline (0.083 g, 0.50 mmol) and 5-amino-1-benzylbenzimidazole (0.112 g, 0.50 mmol) were reacted in 2-propanol (10 ml) according to the General

Procedure. The desired compound was collected by filtration as a yellow solid (0.073 g, 38%); m/z $(M + 1)^+$ 352; δH (d_6-DMSO) 9.35 (IH,s), 8.95 (IH,d), 8.9 (1H, s), 7.7-8.2 (6H, m), 7.3-7.5 (5H,m), 5.7 (2H,s).

Example 19

4-(2-Benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.480 g, 2.006 mmol) and an isomeric mixture of 1-, 2- and 3-benzyl-5-aminobenzotriazole (0.450 g, 2.006 mmol) were reacted in acetonitrile (30ml) according to the General Procedure. The mixture was cooled and the yellow precipitate collected by filtration. This material was then chromatographed on silica gel (Merck 9385, 70 g). Elution with $CH_2 Cl_2$: EtOH:NH_3 200:8:1 gave a blue-green solid (0.139 g, 17%); LC/MS - single isomer $(M + 1)^+$ 413; δH (d_6-DMSO) 9.65 (1H, s), 8.51 (IH,s), 8,48 (IH.,s), 7.91 (1H, d), 7.87 (IH,s), 7.75 (IH,d), 7.3-7.4 (5H,m), 7.20 (IH,s), 5.92 (2H,s), 3.97 (6H, 2 x s).

Also isolated in this chromatography was a pale green solid (0.262 g, 32 %) shown by LC/MS to be 2 isomers (both different to the first isolated) and both with $(M + 1]^+$ 413

By nmr the major isomer was assigned as 4-(1-benzyl -5-benzotriazolylamino)-6,7-dimethoxyquinazoline and the minor isomer was assigned as 4-(3-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline.

Major isomer δH (d_6-DMSO) 9.68 (IH,s), 8.48 (IH,s), 8.45 (IH,s), 7.86 (IH,s), 7.82 (2H,s), 7.3-7.4 (5H,m), 7.19 (IH,s). 5.96 (2H,s), 3.97 (6H, 2 x s).

Minor isomer δH (d_6-DMSO) 9.72 (IH,s), 8.49 (1H,s), 8.37 (IH,d), 8.02 (IH,d), 7.86 (IH,s), 7.71 (IH,dd), 7.3-7.4(5H,m), 7.20 (IH,s), 5.93 (2H, s), 3.97 (6H, 2 x s).

The isomers were assigned by means of the nuclear Overhauser effect.

Example 20

4-(2-Phenethyl-5-indazolylamino)-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.189 g, 0.842 mmol) and an isomeric mixture of 1- and 2-phenethyl-5-aminoindazole (0.200 g, 0.842 mmol) were reacted in acetonitrile (15 ml) according the General Procedure. On cooling a pale yellow precipitate was formed which was collected by filtration. This material was chromatographed on silica gel (Merck 9385, 45 g). Elution with CH_2Cl_2 : EtOH:NH_3 200:8:1 gave a pale green foam (0.039 g, 11%); m/z $[M + 1]^+$ 426; δH ($CDCl_3$) 8.66 (IH,s), 8.05 (2H,s), 7.78 (IH,s), 7.69 (IH,s), 7.03-7.41 (6H, m), 4.64 (2H, t), 4.02 (6H, 2 x s), 3.32 (2H, t).

Also isolated from this chromatography was 4-(1-phenethyl-5-indazoylamino)-6,7-dimethoxyquinazoline (0.145 g, 40%) as a colourless foam; m/z $[M + 1]^+$ 426; δH ($CDCl_3$) 8.63 (IH,s), 8.00(2H, 2 x s), 7.49 (IH,d), 7.1-7.3 (7H, m), 7.04 (IH,s), 4.60 (2H, t) 4.03 (6H, 2 x s), 3.23 (2H, t).

Example 21

4-(2-(2-Pyridyl)-5-benzimidazolylamino)-quinazoline hydrochloride

4-Chloroquinazoline (0.063 g, 0.38 mmol) and 5-amino-2-(2-pyridyl)-benzimidazole (0.080 g, 0.38 mmol) were reacted in 2-propanol (5 ml) according to the General Procedure. The desired product was obtained by filtration as a yellow solid (0.072 g, 50%); m/z ($M + 1^+$) 339; δH (d_6-DMSO) 8.93 (IH,s), 8.88 (IH,d), 8.78 (IH,d), 8.38 (IH,d), 7.86-8.15 (5H,m), 7.75 (IH,d), 7.55-7.64 (2H,m).

Example 22

4-(2-Benzylsulphonyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.112 g, 0.497mmol) and 5-amino-2-benzylsulphonylbenzimidazole (0.143 g, 0.497 mmol) were reacted in acetonitrile (15 ml) according to the General Procedure. On cooling, a yellow precipitate was formed which was collected by filtration. This material was chromatographed on silica gel (Merck 9385, 35 g) Gradient elution with CH_2Cl_2: EtOH:NH_3 100:8:1 to 10:8:1 gave a yellow solid (0.103 g, 44%); m/z $(M+1)^+$ 476; δH (d_6-DMSO) 8.61 (1H, s), 7.7-8.2(4H, m), 7.0-7.4 (6H, m), 5.04 (2H, s), 4.02 (6H, 2 x s).

Biological Data

Compounds of the present invention were tested for protein tyrosine kinase inhibitory activity in a substrate phosphorylation assay and a cell proliferation assay.

The substrate phosphorylation assay uses a baculovirus expressed, recombinant construct of the intracellular domain of c-erbB-2 that is constitutively active. The method measures the ability of the isolated enzyme to catalyse the transfer of ^{33}P-labelled γ-phosphate from ATP onto tyrosine residues in a synthetic peptide. The enzyme is incubated for 1 hour, at room temperature, with 100μM ATP, 10mM $MnCl_2$, 1mg/ml PolyGluAlaTyr (6:3:1) and test compound (diluted from a 5mM stock in DMSO, final DMSO concentration is 2%) in 40mM HEPES buffer, pH 7.4. The reaction is stopped by the addition of EDTA (final concentration 0.1M) and the peptide is then precipitated onto ion exchange filter paper and the incorporated radioactivity determined. Inhibition of the c-erbB-2 kinase is compared against EGF-R TK activity, measured in the same assay method, using solubilised A431 membranes as a source of enzyme activity. The results are shown in Table 1 below as the IC_{50} values in μM.

Table 1

Example	c-erbB-2	EGF-r
1	0.26μM	74% inhibition at 10μM
2	0.016μM	ca 10μM
3	ca 30μM	0.3μM
4	3.4μM	0.003μM

The cell proliferation assay uses an immortalised human breast epithelial cell line (HB4a) which has been transformed by over-expression of c-erbB-2. Growth of th se cells in low serum is dependent upon the c-erbB-2 tyrosine kinase activity. The specificity of the effect of the test compounds on tyrosine kinase dependent growth over general toxicity is assessed by comparison to an HB4a cell line which has been transfected with ras. Cells are plated at 3000/well in 96-well plates in

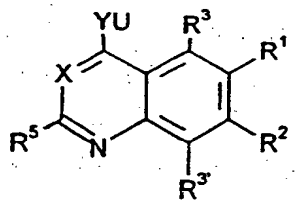
0.1 ml medium and allowed to attach overnight. test compound is added in 0.1 ml medium, with a final concentration of 0.5% DMSO, and the plates incubated for 4 days at 37°C. The cells are then examined microscopically for evidence of morphological detransformation and cell mass is estimated by staining with methylene blue and measuring the absorbance at 620nm. The results are shown in Table 2 below as the IC_{50} values in μM.

Table 2

Compound of Example	c-erbB-2 (TM)
1	1.3
2	0.3
5	2.2
6	1.3
7	3.1 and 0.29 respectively
8	0.57
9	0.19
10	3.7
11	3.2
12	1
13	6.2
14	7
15	>5
16	1.5
17	21
18	27
19	12 and 9.4 respectively
20	8.0 and 2.9 respectively
21	>50
22	20

Claims

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein;
X is N or CH;
Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group;
U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S, wherein the ring system is substituted by at least one independently selected R^6 group and is optionally substituted by at least one independently selected R^4 group;
R^1, R^2, R^3 and $R^{3'}$ are the same or different and are each selected from amino, hydrogen, halogen, hydroxy, nitro, carboxy, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkoxyl, C_{4-8} alkylcyclo alkoxy, C_{1-8} alkoxycarbonyl, N-C_{1-4} alkylcarbamoyl, N,N-di-[C_{1-4} alkyl]carbamoyl, hydroxyamino, C_{1-4} alkoxyamino, C_{2-4} alkanoyloxyamino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-C_{1-4} alkylpiperazin-1-yl, C_{1-8} alkylthio, arylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, arylsulphonyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{2-4} alkanoyloxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, carboxy-C_{1-4} alkyl, C_{1-4} alkoxycarbonyl-C_{1-4}-alkyl,carbamoyl-C_{1-4} alkyl, N-C_{1-4} alkylcarbamoyl-C_{1-4}alkyl, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4}alkyl, amino-C_{1-4} alkyl, C_{1-4} alkylamino-C_{1-4} alkyl, di-[C_{1-4} alkyl]amino-C_{1-4} alkyl, piperidino-C_{1-4} alkyl, morpholino-C_{1-4} alkyl, piperazin-1-yl-C_{1-4} alkyl, 4-C_{1-4}

alkylpiperazin-1-yl-C_{1-4} alkyl, hydroxy-C_{2-4} alkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkoxy-C_{1-4} alkyl, hydroxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, hydroxy-C_{2-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylthio-C_{1-4} alkyl, phenoxy-C_{1-4} alkyl, anilino-C_{1-4} alkyl, phenylthio-C_{1-4} alkyl, cyano-C_{1-4} alkyl, halogeno-C_{2-4} alkoxy, hydroxy-C_{2-4} alkoxy, C_{2-4} alkanoyloxy-C_{2-4} alkoxy, C_{1-4} alkoxy-C_{2-4} alkoxy, carboxy-C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl-C_{1-4} alkoxy, carbamoyl-C_{1-4} alkoxy, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkoxy, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkoxy, amino-C_{2-4} alkoxy, C_{1-4} alkylamino-C_{2-4} alkoxy, di-[C_{1-4} alkyl]amino-C_{2-4} alkoxy, C_{2-4} alkanoyloxy, hydroxy-C_{2-4} alkanoyloxy, C_{1-4}alkoxy-C_{2-4} alkanoyloxy, phenyl-C_{1-4} alkoxy, phenoxy-C_{2-4} alkoxy, anilino-C_{2-4} alkoxy, phenylthio-C_{2-4} alkoxy, piperidino-C_{2-4} alkoxy, morpholino-C_{2-4} alkoxy, piperazin-1-yl-C_{2-4} alkoxy, 4-C_{1-4} alkylpiperazin-1-yl-C_{2-4} alkoxy, halogeno-C_{2-4} alkylamino, hydroxy-C_{2-4} alkylamino, C_{2-4} alkanoyloxy-C_{2-4} alkylamino, C_{1-4} alkoxy-C_{2-4} alkylamino, carboxy-C_{1-4} alkylamino, C_{1-4} alkoxycarbonyl-C_{1-4} alkylamino, carbamoyl-C_{1-4} alkylamino, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkylamino, amino-C_{2-4} alkylamino, C_{1-4} alkylamino-C_{2-4} alkylamino, di-[C_{1-4}alkylamino-C_{2-4} alkylamino, phenyl-C_{1-4} alkylamino, phenoxy-C_{2-4} alkylamino, anilino-C_{2-4} alkylamino, phenylthio-C_{2-4} alkylamino, C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkylsulphonylamino, benzamido, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halogeno-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoylamino, C_{1-4} alkoxy-C_{2-4} alkanoylamino, carboxy-C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonyl-C_{2-4} alkanoylamino, carbamoyl-C_{2-4} alkanoylamino, N-C_{1-4} alkylcarbamoyl-C_{2-4} alkanoylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{2-4} alkanoylamino, amino-C_{2-4} alkanoylamino, C_{1-4} alkylamino-C_{2-4} alkanoylamino or di-[C_{1-4} alkyl]amino-C_{2-4} alkanoylamino, and wherein said benzamido or benzenesulphonamido substitutent or any anilino, phenoxy or phenyl group on a R^1 substituent may optionally bear one or two halogeno, C_{1-4}alkyl or C_{1-4}alkoxy substituents;

or any adjacent pair of R^1, R^2, R^3 and $R^{3'}$ together form an optionally substituted methylenedioxy or ethylenedioxy group;
each R^4 is independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, di-[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, di-[C_{1-4} alkyl] carbamoyl, carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro or trifluoromethyl;
R^5 is hydrogen, halogen, trifluoromethyl, C_{1-4} alkyl or C_{1-4} alkoxy;
each R^6 is independently a group ZR^7 wherein Z is joined to R^7 through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, V(CRR'), V(CHR) or V where R and R' are each C_{1-4} alkyl and in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, CH(OH), sulphonamide, amide, O, $S(O)_m$ or NR^b where R^b is hydrogen or R^b is C_{1-4} alkyl; and R^7 is an optionally substituted C_{3-6} cycloalkyl; or an optionally substituted 5, 6, 7, 8, 9 or 10 membered carbocyclic or heterocyclic moiety;

or R^6 is a group ZR^7 in which Z is NR^b, and NR^b and R^7 together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety.

2. A compound as claimed in claim 1, wherein R^1, R^2 and R^3 are each selected from amino, hydrogen, halogen, hydroxy, nitro, C_{1-8} alkyl, C_{1-8} alkoxy C_{1-8} alkylthio, C_{1-4} alkylamino, or R^1 and R^2 or R^1 and R^3 together form an optionally substituted methylenedioxy or ethylenedioxy group; $R^{3'}$ is hydrogen
R^4 is hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, di-[C_{1-4} alkyl]amino, nitro or trifluoromethyl;
R^5 is hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;
Z is absent or represents CH_2, oxygen, $S(O)_m$ wherein m is 0, 1 or 2, or NR^b wherein R^b is hydrogen, or R^b is C_{1-4} alkyl, and
R^7 is an optionally substituted phenyl, benzyl, pyridyl, dioxolanyl, phenoxy, benzyloxy, phenylamino, benzylamino, phenymercapto or benzylmercapto

group, preferably a phenyl, fluorophenyl, pyridyl, 1,3-dioxolanyl or benzyl group.

3. A compound as claimed in claim 1 or 2, wherein R^1, R^2 and R^3 are each selected from hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy or together form a methylenedioxy or ethylenedioxy group.

4. A compound as claimed in claim 1, 2 or 3, wherein R^6 is in the ring which is remote from Y when U represents a bicyclic group.

5. A compound as claimed in claim 1, 2, 3 or 4, wherein X is N.

6. A compound as claimed in any preceding claim, wherein Y is NR^b, $NR^b(CH_2)$, or $(CH_2)NR^b$, preferably Y is NR^b.

7. A compound as claimed in any preceding claim, wherein U represents an indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group.

8. A compound as claimed in any preceding claim, wherein R^6 is phenyl, fluorophenyl, phenethyl, benzyl, pyridyl, phenylsulphonyl, benzylsulphonyl, phenoxy, benzyloxy or 1,3-dioxolanyl.

8. A compound as claimed in any preceding claim, wherein R^1 and R^2 are independently hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy.

9. A compound as claimed in claim 1 selected from the group comprising:
4-(1-benzyl-5-indolylamino)quinazoline;
4-(1-benzyl-5-indolylamino)-6,7-dimethoxyquinazoline;
4-(2-benzyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
4-(2-benzyl-5-benzimidazolylamino)-quinazoline;
4-(2-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;

4-(1-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indazolylamino)-quinazoline;
4-(1-phenylsulphonyl-5-indolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-2,3-dihydroindolyl-5-amino)-6,7-dimethoxyquinazoline;
4- [3-(4-fluorophenyl)-6-indazolylamino]-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indolylamino)-6,7-diethoxyquinazoline;
4-[1-[2-(1,3-dioxolan-2-yl)-ethyl]-5-indazolylamino]-6,7-dimethoxyquinazoline;
4-(1-benzyl-6-indolyamino)-6,7-dimethoxyquinazoline;
4-(2-phenyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indolylamino)-6,7-methylenedioxyquinazoline;
4-(3-benzyl-5-benzimidazolylamino)-quinazoline;
4-(1-benzyl-5-benzimidazolylamino)-quinazoline;
4-(2-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(3-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(2-phenethyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-phenethyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(2-(2-pyridyl)-5-benzimidazolylamino)-quinazoline;
4-(2-benzylsulphonyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
and salts thereof, particularly pharmaceutically acceptable salts thereof.

10. A compound as claimed in claim 1 selected from the group comprising:
4-(2-benzyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
4-(2-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indazolylamino)-quinazoline;
4-(1-phenylsulphonyl-5-indolylamino)-6,7-dimethoxyquinazoline;
and pharmaceutically acceptable salts thereof.

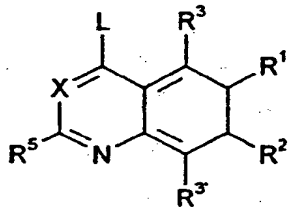
11. Method of treatment of the human or animal body suffering from a disorder mediated by aberrant tyrosine kinase activity which comprises

administering an effective amount of a compound of formula (I), or a physiologically acceptable salt thereof, to the human or animal patient.

12. Pharmaceutical formulation comprising one or more compounds of formula (I), or pharmaceutically acceptable salt(s) thereof, together with one or more pharmaceutically acceptable carriers.

13. A unit dosage form containing a compound of formula (I) or a physiologically acceptable salt thereof in an amount from 70 to 700 mg.

14. Method of making a compound of formula (1), the method including the step of reacting a compound of formula (II):



(II)

with a compound of formula (III):

UYH (III)

where L is a leaving group and U, X, Y and R^1 to R^6 are as defined in claim 1.

15. A method as claimed in claim 13, the method including the step of transforming a compound of formula (I) into another compound of formula (I).

16. A compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

17. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of malignant tumours.

18 Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of atherosclerosis, restenosis or thrombosis.

INTERNATIONAL SEARCH REPORT

Inte. nal Application No
PCT/EP 96/03026

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/12 C07D401/14 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 15758 (RHONE-POULENC RORER) 15 June 1995 see page 15; claims ---	1,12-18
A	EP,A,0 602 851 (ZENECA) 22 June 1994 cited in the application see claims --- -/--	1,12-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 1996	17.10.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 96/03026

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 95, no. 1, 1981 Columbus, Ohio, US; abstract no. 7199s, V.K. AGRAWAL ET AL.: "STUDIES IN POTENTIAL FILARICIDES :PARTXI." page 68682; XP002015687 see abstract	1,12-18
A	& INDIAN J. CHEM.,SECT. B, vol. 19B, no. 12, 1980, ENGL., pages 1084-1087, ---	1,12-18
P,X	WO,A,96 15118 (ZENECA) 23 May 1996 see the whole document -----	1,12-18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I ıational application No.
PCT/EP 96/03026

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of the human body, the search has been carried out and based on the attributed effects of the compounds (Rule 39.1 (iv)-PCT).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

..nformation on patent family members

Inter nal Application No
PCT/EP 96/03026

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9515758	15-06-95	US-A-	5480883	02-01-96
		AU-A-	1305095	27-06-95
EP-A-602851	22-06-94	AU-B-	664496	16-11-95
		AU-A-	5072893	23-06-94
		CA-A-	2103383	11-06-94
		CN-A-	1094043	26-10-94
		CZ-A-	9302651	15-06-94
		FI-A-	935431	11-06-94
		HU-A-	65622	28-07-94
		JP-A-	6336481	06-12-94
		NO-A-	934504	13-06-94
		NZ-A-	250218	25-06-96
		ZA-A-	9308594	10-06-94
WO-A-9615118	23-05-96	AU-A-	3813095	06-06-96